UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,242	03/21/2001	Robert Haselbeck	ELITRA.011A	7191

210 7590 06/29/2010

MERCK
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
06/29/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/815,242	HASELBECK ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,31,45-69,77-87,89-96,100,101,103 and 104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,31,45-69,77-86,89-96,100,101 and 103* is/are rejected.

7)☐ Claim(s) *87 and 104* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner handling this application has changed. Please address further correspondence to Richard Schnizer, Art Unit 1635, whose contact information is given at the end of this Action.

An amendment was received and entered on 9/22/09, and a response to a request for information under 37 CFR 1.105 was received on 3/19/10.

Claims 12, 31, 45-69, 77-87, 89-96, 100, 101, 103, and 104 remain pending and under consideration. The elected species of invention under consideration is a method as set forth in independent claims 12, 31, and 100, wherein the species of prokaryotic organism is S. aureus (Applicant's response of 6/30/03).

Election/Restrictions

Applicant's arguments filed 9/22/09 are persuasive with regard to SEQ ID NOS: 8502 and 5283, and these sequences are rejoined. Applicant also argues that SEQ ID NOS: 1390, 1845, 2782, and 3283 should also be examined because they are part of the larger molecule represented by SEQ ID NO: 4228 (elected) and so should not provide too great a burden. This is unpersuasive. Due to the extremely large number of hits obtained when searching SEQ ID NO: 4228, an effective search of these specific sequences requires a separate search query of multiple databases for each SEQ ID. As explained previously in the Actions of 8/22/02, 6/3/03, and 9/23/03, these searches present an undue burden on the Office due to the complex nature of the searches and the amount of processor time taken by each search.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, e.g. at page 5, lines 18 and 19; page 76, line 11; page 90, lines 1, 4, 12, 14, 15, 17,and 18; and page 185, line 1. Applicant is required to delete all embedded hyperlinks and/or other forms of browser-executable code. See MPEP § 608.01.

Claim Objections

The listing of the claims is objected to because it does not account for claim 102, which was canceled on 2/14/05. Appropriate correction is required.

Claims 87 and 104 are objected to because they recite non-elected subject matter (SEQ ID NOS: 1390, 1845, 2782, and 3283).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12, 31, 45-52, 57, 85, 86, 89-92, and 101 are rejected under 35 U.S.C. 102(b) as being anticipated by Vermuelen et al (US 5872104) as evidenced by Schaefer et al (J. Bact. 188(23): 8252-8258, 2006).

Vermuelen taught a method of sensitizing bacteria to the effects of an antibiotic by inhibiting the expression of bacterial methylases through the use of antisense, and then contacting the sensitized bacteria with an antibiotic. See abstract; Example II at columns 32 and 33; and Example XII at columns 67-70. In particular, Example II describes how different combinations of sensitizing agents and antibiotics are screened. In one test, no sensitizing compound is added (sentence bridging columns 32 and 33. Organisms in which this method can be performed include S. aureus and coagulase negative staphylococci (see entire document , e.g. Table 6 column 29; and Table 7 at column 30).

Note that the instant claims require no structural nexus between the recited antisense nucleic acid and instant SEQ NO: 1463. The claims require that the antisense nucleic acid must be complementary to a portion of a nucleic acid that encodes a gene product, wherein that gene product or its activity is reduced by an antisense nucleic acid comprising any nucleotide sequence in SEQ ID NO: 1463. SEQ ID NO: 1463 inhibits the expression of S. aureus yphC (Applicant's response of 9/22/09 at page 15) which encodes a GTPase required for the assembly of the large ribosomal subunit (see Schaefer (2006)). Thus the expected effect of treating a prokaryotic cell SEQ ID NO: 1463 would be to decrease the expression of yphC protein, resulting in inhibition of ribosome synthesis, and a decrease in expression and activity of all protein gene products. In other words, the expression, and subsequently the activity, of all S. aureus protein gene products, including the methylases of Vermuelen, is inhibited by SEQ ID 1463. So, Vermuelen taught a method of screening for antibiotics by providing

to an S. aureus, or coagulase negative staphylococcus, varying non-lethal amounts of an antisense that inhibits the expression or activity of a methylase enzyme. This produces sensitized bacteria. The sensitized bacteria are contacted with a variety of antibiotics to determine which combination of antisense and antibiotic kills bacteria most efficiently. Because the methylase enzyme must be produced by ribosome-driven translation, it is a gene product whose expression and activity are inhibited by SEQ ID NO: 1463 because the gene product inhibited by SEQ ID NO: 1463 is required for translation of any and all S. aureus proteins.

Thus Vermuelen teaches each and every limitation of the invention and anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 12, 31, 45-69, 77-86, 89-96, 100, and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zalacain et al (WO 01/23418), Fritz et al (US 6627747), Zhang et al (Gene 255: 297-305, 2000), and Ji et al (J. Bact. 181(21): 6585-6590, 1999).

Zalacain disclosed yphC gene and polypeptide from S. aureus, and suggested that yphC could be used as a target for the development of antibiotics (page 2, lines 5-

12; and page 16, line 10 to page 22, line 9). Zalacain also showed that yphC was essential for growth in S. aureus by allelic replacement in strain RN4220 (page 32, lines 15-30). The Zalacain publication designates the United States and claims priority to Non-Provisional Application 09/406,968, filed 9/28/1999. The information relating to Zalacain that is used in this rejection is completely supported by the '968 application and is entitled to a filing date of 9/28/1999.

Fritz taught that yphC was an essential GTPase in S. pneumoniae, that the gene was conserved and essential in other bacteria, such as B. subtilis and E. coli, and suggested screening for inhibitors of yphC because such inhibitors would have a broad spectrum of antibiotic activity. See abstract; paragraph bridging columns 13 and 14; column 16, lines 34-50; and column 19, lines 49-60. Fritz suggested testing candidate YphC inhibitors to determine if they can inhibit bacterial growth (see column 26, lines 33 to 47 and column 28, lines 41-57.

These references did not teach a method of screening for antibiotics in which bacterial cells were sensitized to the effects of a potential antibiotic by decreasing the amount or activity of yphC.

Zhang taught methods and systems for determining gene essentiality in bacteria, and for determining if the mode of action of an antibiotic involves a given essential gene. The methods rely on systems that allow one to modulate the level of expression of a known or suspected essential gene. Regulatable expression systems were developed that exhibit titratable induction of expression. By using these systems to vary the amount of expression of an essential gene in a bacterium such as S. aureus or

Bacillus subtilis, and treating the bacterium with a candidate antibiotic, one can determine if any growth inhibition caused by the antibiotic is due to a mode of action involving the essential gene. This can be done by varying the amount of expression of a particular essential gene in separate cultures, and then determining the minimum inhibitory concentration of a candidate antibiotic in each culture. If the function of an antibiotic involves the targeted essential gene, then the sensitivity of the cells to the antibiotic will vary inversely with the amount of the gene that is expressed. See abstract and section 3.3 on pages 302-304. Cell growth rates were measured by monitoring optical density at 600 nm (section 2.7 on page 300). Strains used included S. aureus RN4220 (section 2.1 on page 298).

It would have been obvious to one of ordinary skill in the art at the time of the invention to screen for yphC inhibitors because both Zalacain and Fritz taught that yphC was a target for antibiotic development. One would have been motivated to use the method of Zhang because it allows one to determine if the cellular activity of an antibiotic is occurring through its proposed molecular target as opposed to some other mechanism. Moreover, yphC was known to be essential in S. aureus, S. pneumoniae, B. subtilis, and E. coli (see Zalacain at page 32, lines 15-30; and Fritz at columns 13 and 14; column 16, lines 34-50; and column 19, lines 49-60) such that inhibitors that act through yphC are expected to be broad spectrum antibiotics.

This method does not involve the use of antisense, as does the instantly claimed method.

Ji taught a method and system for regulated expression of antisense in S. aureus, and showed that gene expression could be efficiently inhibited by expressing antisense in situ in S. aureus RN4220. See abstract.

In view of the teachings of Zhang it was clear that one could determine if a candidate antibiotic was acting through it's intended target by varying the amount of expression of that target in the presence of the antibiotic. It was also clear at the time of the invention that there was more than one way to modulate the expression of an essential gene. Zhang taught a method in which gene expression was controlled by replacing the chromosomal copy of the essential gene with another copy under the control of an inducible promoter. On the other hand Ji taught a method of regulating expression of essential genes in S. aureus by expressing antisense RNA directed against the transcript of the essential gene. Thus it would have been clear to one of ordinary skill in the art at the time of the invention that one could sensitize cells for screening antibiotics by regulating the expression of yphC negatively, i.e. by using antisense to control the expression of the essential gene, as taught by Ji, instead of using positive control of gene expression, as taught by Zhang. This is simply a matter of design choice. All of the technology required to control gene expression, either positively or negatively, was known in the art, and one of ordinary skill could have chosen either approach and achieved the same end, i.e. control over the amount of yphC expressed in the subject S. aureus culture. In using the antisense approach, it would have been obvious to refer to the prior art sequence of Zalacain to obtain an antisense sequence. Instant SEQ ID NO: 1463 is 100% complementary to nucleotides

122-508 of the yphC sequence of Zalacain, see alignment below. Accordingly, the antisense obtained would necessarily downregulate an RNA that can be reduced by antisense comprising a sequence of SEQ ID NO: 1463, as required by claim 12 and dependents.

```
Score =  715 bits (387),  Expect = 0.0
 Identities = 387/387 (100%), Gaps = 0/387 (0%)
 Strand=Plus/Minus
"Query" = yphC DNA sequence from Zalacain
"Subject" = complement of instant SEQ IDNO: 1463

Query  122  GTATTTATTCTTCAGGTGAATGGTTAACACATGATTTCAATATTATTGATACAGGTGGTA  181
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  387  GTATTTATTCTTCAGGTGAATGGTTAACACATGATTTCAATATTATTGATACAGGTGGTA  328

Query  182  TTGAAATTGGTGATGCACCATTCCAAACACAAATTAGAGCGCAGGCAGAAATCGCCATAG  241
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  327  TTGAAATTGGTGATGCACCATTCCAAACACAAATTAGAGCGCAGGCAGAAATCGCCATAG  268

Query  242  ATGAAGCGGATGTTATTATTTTTATGGTTAACGTGCGTGAAGGATTGACACAAAGCGATG  301
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  267  ATGAAGCGGATGTTATTATTTTTATGGTTAACGTGCGTGAAGGATTGACACAAAGCGATG  208

Query  302  AAATGGTCGCTCAAATTTTATACAAATCTAAAAAACCGGTCGTATTAGCGGTTAACAAAG  361
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  207  AAATGGTCGCTCAAATTTTATACAAATCTAAAAAACCGGTCGTATTAGCGGTTAACAAAG  148

Query  362  TAGATAATATGGAAATGCGTACAGACGTGTATGATTTCTATTCATTAGGATTTGGTGAAC  421
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  147  TAGATAATATGGAAATGCGTACAGACGTGTATGATTTCTATTCATTAGGATTTGGTGAAC  88

Query  422  CGTATCCGATATCAGGGTCACATGGTTTAGGTCTTGGTGACTTGTTAGATGCAGTTGTTT  481
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  87   CGTATCCGATATCAGGGTCACATGGTTTAGGTCTTGGTGACTTGTTAGATGCAGTTGTTT  28

Query  482  CTCATTTTGGTGAAGAGGAAGAAGATC  508
            |||||||||||||||||||||||||||
Sbjct  27   CTCATTTTGGTGAAGAGGAAGAAGATC  1
```

Moreover, the polypeptide sequence of Zalacain is 100% identical to instant SEQ ID NO: 12600 (see alignment below), which is encoded by instant SEQ ID NO: 8502. Thus one would have inhibited the expression of instant SEQ IDNO: 12600 as intended in instant claims 31, 100, and dependents.

```
 Score =  887 bits (2293),  Expect = 0.0, Method: Compositional matrix
adjust.
 Identities = 436/436 (100%), Positives = 436/436 (100%), Gaps = 0/436 (0%)
"Query" = yphC amino acid sequence from Zalacain
"Subject" = instant SEQ ID NO: 12600

Query  1    MTKPIVAIVGRPNVGKSTIFNRIVGERVSIVEDTPGVTRDRIYSSGEWLTHDFNIIDTGG  60
            MTKPIVAIVGRPNVGKSTIFNRIVGERVSIVEDTPGVTRDRIYSSGEWLTHDFNIIDTGG
Sbjct  1    MTKPIVAIVGRPNVGKSTIFNRIVGERVSIVEDTPGVTRDRIYSSGEWLTHDFNIIDTGG  60

Query  61   IEIGDAPFQTQIRAQAEIAIDEADVIIFMVNVREGLTQSDEMVAQILYKSKKPVVLAVNK  120
            IEIGDAPFQTQIRAQAEIAIDEADVIIFMVNVREGLTQSDEMVAQILYKSKKPVVLAVNK
Sbjct  61   IEIGDAPFQTQIRAQAEIAIDEADVIIFMVNVREGLTQSDEMVAQILYKSKKPVVLAVNK  120

Query  121  VDNMEMRTDVYDFYSLGFGEPYPISGSHGLGLGDLLDAVVSHFGEEEEDPYDEDTIRLSI  180
            VDNMEMRTDVYDFYSLGFGEPYPISGSHGLGLGDLLDAVVSHFGEEEEDPYDEDTIRLSI
Sbjct  121  VDNMEMRTDVYDFYSLGFGEPYPISGSHGLGLGDLLDAVVSHFGEEEEDPYDEDTIRLSI  180

Query  181  IGRPNVGKSSLVNAILGEDRVIVSNVAGTTRDAIDTEYSYDGQDYVLIDTAGMRKKGKVY  240
            IGRPNVGKSSLVNAILGEDRVIVSNVAGTTRDAIDTEYSYDGQDYVLIDTAGMRKKGKVY
Sbjct  181  IGRPNVGKSSLVNAILGEDRVIVSNVAGTTRDAIDTEYSYDGQDYVLIDTAGMRKKGKVY  240

Query  241  ESTEKYSVLRALKAIERSNVVLVVIDAEQGIIEQDKRVAGYAHEQGKAVVIVVNKWDTVE  300
            ESTEKYSVLRALKAIERSNVVLVVIDAEQGIIEQDKRVAGYAHEQGKAVVIVVNKWDTVE
Sbjct  241  ESTEKYSVLRALKAIERSNVVLVVIDAEQGIIEQDKRVAGYAHEQGKAVVIVVNKWDTVE  300

Query  301  KDSKTMKKFEDEVRKEFQFLDYAQIAFVSAKERTRLRTLFPYINEASENHKKRVQSSTLN  360
            KDSKTMKKFEDEVRKEFQFLDYAQIAFVSAKERTRLRTLFPYINEASENHKKRVQSSTLN
Sbjct  301  KDSKTMKKFEDEVRKEFQFLDYAQIAFVSAKERTRLRTLFPYINEASENHKKRVQSSTLN  360

Query  361  EVVTDAISMNPTPTDKGRRLNVFYATQVAIEPPTFVVFVNDVELMHFSYKRYLENQIRAA  420
            EVVTDAISMNPTPTDKGRRLNVFYATQVAIEPPTFVVFVNDVELMHFSYKRYLENQIRAA
Sbjct  361  EVVTDAISMNPTPTDKGRRLNVFYATQVAIEPPTFVVFVNDVELMHFSYKRYLENQIRAA  420

Query  421  FGFEGTPIHIIARKRN  436
            FGFEGTPIHIIARKRN
Sbjct  421  FGFEGTPIHIIARKRN  436
```

Claims 78-84 require that the antisense nucleic acid used to reduce the amount or activity of the recited gene product must comprise a sequence with at least 70-97% nucleotide sequence identity to SEQ ID NO: 1463. These claims are included in the rejection because it would have been obvious to one of ordinary skill in the art at the time of the invention to use the entire coding sequence of yphC to generate an antisense transcript, i.e. to use an antisense complementary to the entire length of the yphC transcript. In so doing one would obtain an antisense transcript comprising SEQ

ID NO: 1463. Moreover, the claims as written do not specify the length of the sequence that must share identity with SEQ ID NO: 1463, such that an antisense molecule with as few as two nucleotides of SEQ ID NO: 1463 "comprises a sequence having at least 97% nucleotide sequence identity to SEQ ID NO: 1463." SEQ ID NO: 1463 contains all 16 possible dinucleotide sequences, so any antisense directed to yphC will contain at least one dinucleotide that is 100% identical to SEQ ID NO: 1463. Because the cited references render obvious antisense directed to the yphC sequence of Zalacain, they render obvious an antisense nucleic acid as required by instant claims 78-84.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed. Claims 87 and 104 are objected to because they recite non-elected subject matter and depend from rejected claims, but would be allowable if rewritten in independent form excluding the nonelected subject matter and incorporating all of the limitations of the claims from which they depend.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Fereydoun Sajjadi, can be reached at (571) 272-3311. The official central

fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635